Complete Summary

GUIDELINE TITLE

American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor–positive breast cancer: status report 2004.

BIBLIOGRAPHIC SOURCE(S)

Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, Chlebowski RT, Gelber R, Edge SB, Gralow J, Cobleigh MA, Mamounas EP, Goldstein LJ, Whelan TJ, Powles TJ, Bryant J, Perkins C, Perotti J, Braun S, Langer AS, Browman GP, Somerfield MR. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol 2005 Jan 20;23(3):619-29. [50 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Winer EP, Hudis C, Burstein HJ, Chlebowski RT, Ingle JN, Edge SB, Mamounas EP, Gralow J, Goldstein LJ, Pritchard KI, Braun S, Cobleigh MA, Langer AS, Perotti J, Powles TJ, Whelan TJ, Browman GP. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: status report 2002. J Clin Oncol 2002 Aug 1;20(15):3317-27.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Breast cancer

GUIDELINE CATEGORY

Prevention
Risk Assessment
Technology Assessment
Treatment

CLINICAL SPECIALTY

Obstetrics and Gynecology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To update the 2003 American Society of Clinical Oncology technology assessment on adjuvant use of aromatase inhibitors

TARGET POPULATION

Postmenopausal women with hormone receptor-positive breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Use of third-generation aromatase inhibitors/inactivators as adjuvant therapy for hormone receptor-positive breast cancer:
    - Anastrozole (Arimidex)
    - Letrozole
    - Exemestane
2. Standard therapy with tamoxifen
3. Combination therapy of tamoxifen and an aromatase inhibitor

MAJOR OUTCOMES CONSIDERED

- Disease recurrence
- Quality of life and sexual functioning
- Disease-free survival
- Breast cancer incidence
- Breast cancer-specific survival
- Overall survival
- Net health benefit

- Adverse effects of therapy
- Duration of therapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

An updated MEDLINE search was performed; relevant manuscripts and conference presentations were reviewed; and pharmaceutical companies manufacturing a commercially available, third-generation aromatase inhibitor were contacted and asked to provide additional data.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In an effort to provide guidance to patients and physicians, the Technology Assessment Panel chose to address a series of questions concerning the use of the

aromatase inhibitors as adjuvant treatment for women with operable breast cancer.

- Are there new data to prompt a recommendation for an aromatase inhibitor as initial adjuvant therapy in unselected postmenopausal patients with hormone receptor-positive breast cancer?
- Are there specific patient populations that should receive initial therapy with an aromatase inhibitor in lieu of tamoxifen?
- Do the results of the MA-17 Trial provide sufficient evidence to recommend the use of an aromatase inhibitor in postmenopausal women with hormone receptor-positive breast cancer who have completed a 5-year course of tamoxifen?
- Do the results of the Intergroup Exemestane Study (IES) and Italian (ITA) trials provide sufficient evidence to recommend the use of an aromatase inhibitor in postmenopausal women with hormone receptor-positive breast cancer who have received tamoxifen for 2 to 3 years?
- What is the optimal duration of therapy with an aromatase inhibitor in the adjuvant setting?
- Should an aromatase inhibitor be continued for longer than 5 years outside of a clinical trial?
- In women who are switched from tamoxifen to an aromatase inhibitor after 2 to 3 years, should treatment with the aromatase inhibitor continue beyond the 5-year point?
- Are there any studies that support the use of tamoxifen after an aromatase inhibitor?
- Is there any role for the aromatase inhibitors in women with hormone receptor-negative breast cancer?
- Is it reasonable to use an aromatase inhibitor as initial hormonal therapy in a woman who is premenopausal at diagnosis and who appears to have gone through menopause with chemotherapy?
- Is it reasonable to use an aromatase inhibitor in combination with a luteinizing hormone-releasing hormone agonist or oophorectomy in a woman who is premenopausal at diagnosis?
- What is known about bone and musculoskeletal toxicity associated with the aromatase inhibitors?
- What is known about vascular complications and endometrial cancer in women treated on the adjuvant aromatase inhibitors trials?
- What is known about overall quality of life and sexual functioning in women on aromatase inhibitors?
- To what extent can physicians individualize decisions about adjuvant hormonal therapy?
- How can physicians better quantify the risks of relapse and/or second primary in women who have taken a course of tamoxifen for either 2 to 3 or 5 years?

In early 2004, the Technology Assessment Panel met by teleconference to review newly released and published data concerning the use of the aromatase inhibitors in the adjuvant setting. With the availability of new information, the Panel unanimously agreed to develop updated recommendations. The Panel focused on two separate but related topics: (1) evidence to support the substitution of an aromatase inhibitor for tamoxifen as initial adjuvant hormonal therapy in postmenopausal women, and (2) evidence to support switching postmenopausal

women from tamoxifen to an aromatase inhibitor after 5 or fewer years of tamoxifen therapy.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The conclusions of the panel were endorsed by the American Society of Clinical Oncology (ASCO) Health Services Research Committee (HSRC) and the American Society of Clinical Oncology Board of Directors.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Based on results from multiple large randomized trials, adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumor recurrence. Neither the optimal timing nor duration of aromatase inhibitor therapy is established. Aromatase inhibitors are appropriate as initial treatment for women with contraindications to tamoxifen. For all other postmenopausal women, treatment options include 5 years of aromatase inhibitors treatment or sequential therapy consisting of tamoxifen (for either 2 to 3 years or 5 years) followed by aromatase inhibitors for 2 to 3, to 5 years. Patients intolerant of aromatase inhibitors should receive tamoxifen. There are no data on the use of tamoxifen after an aromatase inhibitor in the adjuvant setting. Women with hormone receptor-negative tumors should not receive adjuvant endocrine therapy. The role of other biomarkers such as progesterone receptor and HER2 status in selecting optimal endocrine therapy remains controversial. Aromatase inhibitors are contraindicated in premenopausal women; there are limited data concerning their role in women with treatment-related amenorrhea. The side effect profiles of tamoxifen and aromatase inhibitors differ. The late consequences of aromatase inhibitor therapy, including osteoporosis, are not well characterized.

Conclusion

The Panel believes that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an aromatase inhibitor as

initial therapy or after treatment with tamoxifen. Women with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated. The recommendations were based primarily on the results from four large randomized phase III clinical trials (see original guideline document for details). Testimony was also collected from invited experts and interested parties.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Although only one trial (MA-17) demonstrated a survival advantage associated with the use of an aromatase inhibitor and this only in node-positive patients, the three large studies discussed in this Update show a clear and consistent improvement in disease-free survival among women who received an aromatase inhibitor compared with those who were randomized to a control arm and did not receive one of these agents. At this time, the guideline Panel believes that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer should include an aromatase inhibitor either as initial therapy or after treatment with tamoxifen.

POTENTIAL HARMS

- The long-term side effects of the aromatase inhibitors are not known, and it is possible that the toxicity profile will change with the accumulation of additional data. Some toxicities, such as thromboembolic events and uterine abnormalities, are reduced with the use of an aromatase inhibitor when compared with tamoxifen. There is, however, an increase in osteoporosis and/or in fractures in women receiving the aromatase inhibitors. These findings suggest that close monitoring for bone loss and consideration of proactive treatment will be an important adjunct to the use of any aromatase inhibitor.
- Use of either tamoxifen or an aromatase inhibitor will increase vasomotor symptoms, presenting a clinical management problem.

CONTRAINDICATIONS

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Aromatase inhibitors are contraindicated in premenopausal women.

QUALIFYING STATEMENTS

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- It important to emphasize that guidelines and technology assessments cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result.
- Accordingly, American Society of Clinical Oncology (ASCO) considers adherence to this technology assessment to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, this technology assessment describes the use of procedures and therapies in clinical practice; it cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed. In that guideline and technology assessment development involve a review and synthesis of the latest literature, a practice guideline or technology assessment also serves to identify important questions and settings for further research.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol 2005 Jan 20;23(3):619-29. [50 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Aug 1 (revised 2005 Jan 20)

GUIDELINE DEVELOPER(S)

American Society of Clinical Oncology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society of Clinical Oncology

GUIDELINE COMMITTEE

American Society of Clinical Oncology Aromatase Inhibitors Expert Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Expert Panel Members: Eric P. Winer, MD (Chair), Dana-Farber Cancer Institute; George P. Browman, MD, Tom Baker Cancer Centre, Calgary; Susan Braun, Susan G. Komen Breast Cancer Foundation; John Bryant, PhD, University of Pittsburgh; Harold J. Burstein, MD, PhD, Dana-Farber Cancer Institute; Rowan T. Chlebowski, MD, PhD, Harbor UCLA Medical Center; Melody A. Cobleigh, MD, Rush Presbyterian-St Luke´s Medical Center; Stephen B. Edge, MD, Roswell Park Cancer Institute; Richard D. Gelber, PhD, Dana-Farber Cancer Institute; Lori J. Goldstein, MD, Fox Chase Cancer Center; Julie Gralow, MD, Seattle Cancer Center Alliance; Clifford Hudis, MD, Memorial Sloan-Kettering Cancer Center; James N. Ingle, MD, Mayo Clinic; Amy S. Langer, Patient advocate and educator; former Executive Director, National Alliance of Breast Cancer Organizations (NABCO); Eleftherios P. Mamounas, MD, Aultman Cancer Center; Cheryl L. Perkins, MD, RPH, Susan G. Komen Breast Cancer Foundation; Judy Perotti, Research Advocacy Network; Trevor S. Powles, MD, PhD, Parkside Oncology Clinic, London; Kathleen I. Pritchard, MD, Toronto-Sunnybrook Regional Cancer Center; Timothy J. Whelan, BM, BCh, MSc, Cancer Care Ontario; Antonio C. Wolff, MD, FACP, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Consultant/Advisory Role: Clifford Hudis, AstraZeneca, Novartis, Pfizer; Kathleen I. Pritchard, AstraZeneca, Aventis, Novartis, OrthoBiotech, Pfizer, Roche, YM Biosciences; James N. Ingle, Novartis, Pfizer; Rowan T. Chlebowski, AstraZeneca, Novartis, Pfizer; Julie Gralow,

AstraZeneca, Novartis, Pharmacia/Pfizer; Eleftherios P. Mamounas, AstraZeneca, Pfizer, Novartis; Lori J. Goldstein, Pfizer, Novartis. Honoraria: Clifford Hudis, AstraZeneca; Antonio C. Wolff, AstraZeneca; Kathleen I. Pritchard, AstraZeneca, Novartis, Pfizer, Roche/Genentech; James N. Ingle, Novartis, Pfizer; Rowan T. Chlebowski, AstraZeneca, Novartis, Pfizer; Eleftherios P. Mamounas, AstraZeneca, Pfizer, Novartis; Lori J. Goldstein, Pfizer, Novartis; Timothy J. Whelan, AstraZeneca. Research Funding: Eric P. Winer, AstraZeneca; Clifford Hudis, AstraZeneca, Novartis, Pfizer; Kathleen I. Pritchard, AstraZeneca; Richard Gelber, International Breast Cancer Study Group (IBCSG). Expert Testimony: Kathleen I. Pritchard, Aventis. For a detailed description of these categories, or for more information about American Society of Clinical Oncology's conflict of interest policy, please refer to the Author Disclosure Declaration form and the "Disclosures of Potential Conflicts of Interest" section of Information for Contributors found in the front of every issue.

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GUIDELINE AVAILABILITY

Electronic copies: Available from the American Society of Clinical Oncology (ASCO) Web site.

Print copies: Available from American Society of Clinical Oncology, Health Services Research, 1900 Duke Street, Suite 200, Alexandria, VA 22314.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on February 27, 2003. The information was verified by the guideline developer on March 14, 2003. This NGC summary was updated by ECRI on May 6, 2005. The information was verified by the guideline developer on May 10, 2005.

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